AMENDMENTS TO THE SPECIFICATION

Please replace paragraph **[0011]** beginning on p. 4 with the following:

[0011] In one aspect, the invention provides method of treating systemic lupus erythematosus (SLE) in an individual, comprising administering to the individual an effective amount of an agent which reduces anti-dsDNA antibody in the individual (such as, a dsDNA epitope which specifically binds to an anti-dsDNA antibody from the individual), wherein the administration of the agent results in a sustained reduction of anti-dsDNA antibody, and wherein the sustained reduction is at least about 10% below baseline in the individual (for example, a value of 100 at baseline would drop at least about 10% to about 90). In some embodiments, the sustained reduction is at least about 20% below baseline in the individual. In some embodiments, the sustained reduction is at least about 30% below baseline in the individual. In some embodiments, the sustained reduction is for at least about one month. In some embodiments, the sustained reduction is for at least about two months. In some embodiments, the sustained reduction is for at least about three months. In some embodiments, the sustained reduction is for at least about four months. In some embodiments, the sustained reduction is for at least about five months. In some embodiments, the sustained reduction is for at least about six months. In some embodiments, the sustained reduction is for at least about one year. In some embodiments, the sustained reduction is for at least about two years or longer. Ideally, treatment results in a sustained reduction for years, since SLE is a chronic disease. In some embodiments, the dsDNA epitope is the double-stranded polynucleotide ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) in combination with its complementary strand, particularly the sequence 3'-CACACACACACACACACACA-5'(SEQ ID NO:2), or one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2). The dsDNA epitope is optionally administered in the form of an epitope-presenting carrier. In other embodiments, the dsDNA epitope comprises, or, consists essentially of any of the above.

Please replace paragraph **[0012]** beginning on p. 5 with the following:

[0012] In another aspect, the invention provides a method of treating renal systemic lupus erythematosus (SLE) in an individual, comprising administering to the individual an effective amount of an agent which reduces anti-dsDNA antibody in the individual (such as, a dsDNA epitope which specifically binds to an anti-dsDNA antibody from the individual), wherein the administration of the agent results in a sustained reduction of anti-dsDNA antibody, and wherein the sustained reduction is at least about 10% below baseline in the individual (for example, a value of 100 at baseline would drop at least about 10% to about 90). In some embodiments, the sustained reduction is at least about 20% below baseline in the individual. In some embodiments, the sustained reduction is at least about 30% below baseline in the individual. In some embodiments, the sustained reduction is for at least about one month. In some embodiments, the sustained reduction is for at least about two months. In some embodiments, the sustained reduction is for at least about three months. In some embodiments, the sustained reduction is for at least about four months. In some embodiments, the sustained reduction is for at least about five months. In some embodiments, the sustained reduction is for at least about six months. In some embodiments, the sustained reduction is for at least about one year. In some embodiments, the sustained reduction is for at least about two years or longer. Ideally, treatment results in a sustained reduction for years, since SLE is a chronic disease. In some embodiments, the dsDNA epitope is the double-stranded polynucleotide ~~5' GTGTGTGTGTGTGTGTGTGT 3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) in combination with its complementary strand, particularly the sequence ~~3' CACACACACACACACACACA 5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2), or one of the single-stranded polynucleotides ~~5' GTGTGTGTGTGTGTGTGTGT 3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or ~~3' CACACACACACACACACACA 5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2). The dsDNA epitope is optionally administered in the form of an epitope-presenting carrier. In other embodiments, the dsDNA epitope comprises, or, consists essentially of any of the above.

Please replace paragraph **[0015]** beginning on p. 7 with the following:

[0015] In one embodiment, the levels of circulating anti-dsDNA antibodies in the individual are reduced by administration of an effective amount of a dsDNA epitope, such as the double-stranded polynucleotide ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) and its complementary strand, particularly the sequence ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2) or one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2) to the individual. In another embodiment, the levels of circulating anti-dsDNA antibodies in the individual are reduced by administering to the individual an effective amount of epitope-presenting valency platform molecule, such as the conjugate LJP 394.

Please replace paragraph **[0020]** beginning on p. 10 with the following:

[0020] In one embodiment, the levels of circulating anti-dsDNA antibodies in the individual are reduced and the sustained reduction is maintained by administration of an effective amount of a dsDNA epitope, such as the double-stranded polynucleotide ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) and its complementary strand, particularly the sequence ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2) or one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2) to the individual. In another embodiment, the levels of circulating anti-dsDNA antibodies in the individual are reduced by administering to the

individual an effective amount of epitope-presenting valency platform molecule, such as the conjugate LJP 394.

Please replace paragraph **[0077]** beginning on p. 30 with the following:

[0077] In another aspect, the invention provides a method of treating SLE, including renal SLE, an individual, comprising reducing the levels of circulating anti-dsDNA antibodies in the individual, and maintaining a sustained reduction of the anti-dsDNA antibodies in the individual of at least about 10% below baseline, wherein sustained reduction of the levels of the circulating anti-dsDNA antibodies in the individual results in reduction of incidence of renal flare. In one embodiment, the anti-dsDNA antibodies in the individual are antibodies that specifically bind double-stranded DNA and single-stranded DNA. In one embodiment, the anti-dsDNA circulating antibodies bind either strand or both strands of the double-stranded polynucleotide comprising, consisting of, or consisting essentially of a strand having the sequence ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) and the complementary strand ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2). Optionally, the anti-dsDNA antibodies bind one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or 3'-~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2). In another embodiment, the anti-dsDNA antibodies specifically bind the pentapeptide sequence Asp/Glu-Trp-Asp/Glu-Tyr-Ser/Gly. In some embodiments, the sustained reduction is for at least about 20% below baseline in the individual. In some embodiments, the sustained reduction is for at least about 30% below baseline in the individual. In some embodiments, the sustained reduction is for at least about one month. In some embodiments, the sustained reduction is for at least about two months. In some embodiments, the sustained reduction is for at least about three months. In some embodiments, the sustained reduction is for at least about four months. In some embodiments, the sustained reduction is for at least about five months. In some embodiments, the sustained reduction is for at least about six months. In some

embodiments, the sustained reduction is for at least about one year. In some embodiments, the sustained reduction is for at least about two years or longer.

Please replace paragraph **[0113]** beginning on p. 41 with the following:

[0113] In preferred embodiments, the affinity of the individual's antibodies for the dsDNA epitope(s) (whether measured directly using the epitope itself or using a moiety/epitope the affinity of which may be correlated to the affinity of the epitope used in the carrier) is measured as the apparent equilibrium dissociation constant (K_D') for the dsDNA epitope(s) in the carrier before or upon initiation of treatment is less than about (in some embodiments, less than or equal to about) 1.0 mg IgG per mL. In other embodiments, the K_D' is less than about (in some embodiments, less than or equal to about) any of the following: 0.8; 0.7; 0.6; 0.5; 0.4; 0.3; 0.2; 0.1; 0.09; 0.08; 0.07; 0.06; 0.05; 0.025. In some embodiments, K_D' is less than about (in some embodiments, less than or equal to about) 0.8 mg IgG per mL. In some embodiments, K_D' is less than or equal to about (in some embodiments, less than or equal to about) 0.5 mg IgG per mL. In some embodiments, K_D' is less than about (in some embodiments, less than or equal to about) 0.1 mg IgG per mL. In some embodiments, the dsDNA epitope used comprises, consists essentially of, or consists of the double-stranded polynucleotide ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) in combination with its complementary strand, particularly the sequence ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2), or one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2), and the initial K_D' is less than about 0.8 mg IgG per ml (in some embodiments, less than or equal to 0.8 mg IgG per ml). In some embodiments, the therapeutic moiety is LJP 394.

Please replace paragraph **[0130]** beginning on p. 48 with the following:

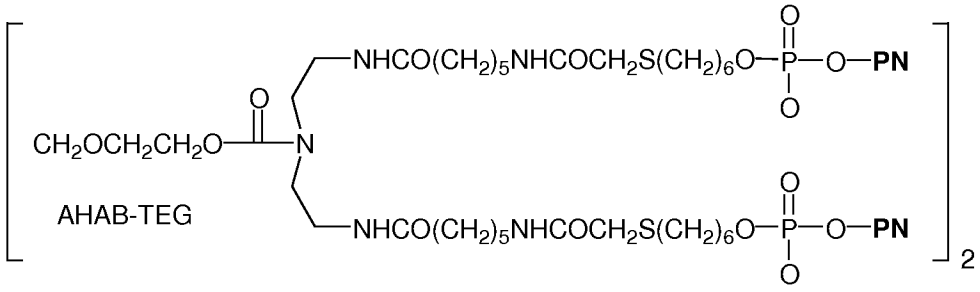
[0130] For instance, optionally, the polynucleotide is double-stranded DNA. In some embodiments, the polynucleotide comprises, consists essentially of, or consists of the double-stranded sequence ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) in combination with the complementary polynucleotide sequence, particularly the sequence ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2).

Please replace paragraph **[0131]** beginning on p. 49 with the following:

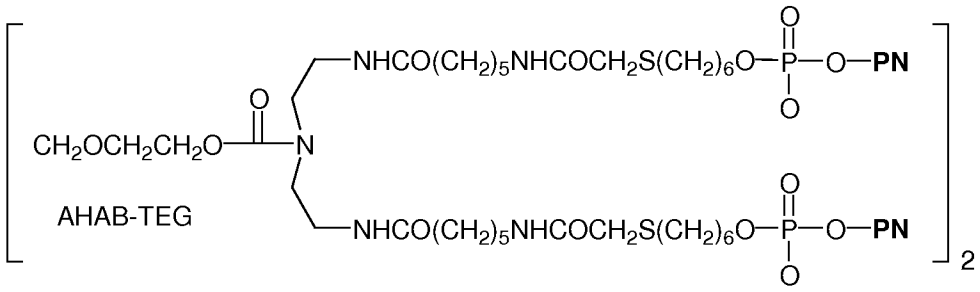
[0131] In some embodiments, the polynucleotide is single-stranded DNA comprising, consisting essentially of, or consisting of the sequence ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1). In some alternative embodiments, the polynucleotide is single-stranded DNA comprising, consisting essentially of, or consisting of the sequence ~~3'-CACACACACACACACACACA-5'(SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2). In another embodiment, the dsDNA epitope comprises, consists essentially of, or consists of the pentapeptide sequence Asp/Glu-Trp-Asp/Glu-Tyr-Ser/Gly.

Please replace paragraph **[0177]** beginning on p. 63 with the following:

[0177] A description of the synthesis of the conjugate LJP 394, a tetravalent conjugate, is described in Jones et al. (1995) and in U.S. Patent 5,552,391, which are hereby incorporated by reference. LJP 394 comprises four 20-mer oligonucleotides consisting of alternating C and A nucleotides, $(CA)_{10}$ 5'-$(CA)_{10}$-3' (SEQ ID NO:2), attached to a platform and annealed with complementary 20-mer oligonucleotides consisting of alternating G and T nucleotides, [[$(GT)_{10}$]] 5'-$(TG)_{10}$-3' (SEQ ID NO:1), oligonucleotide. The valency platform molecule used in LJP 394 is shown immediately below. In one embodiment, the platform molecule is



wherein PN is the polynucleotide. Accordingly, the epitope-presenting valency platform molecule administered to individuals with SLE in any of the methods of the invention described herein is LJP394 (also referred to as "Riquent"^{TM}), which comprises a molecule of the following formula:



wherein PN is $(CA)_{10}$•$(TG)_{10}$ ((SEQ ID NO:2)•(SEQ ID NO:1))

Please replace paragraph **[0181]** beginning on p. 66 with the following:

[0181] In some embodiments, the kits may also contain supplies and instructions for measuring antibody affinities for use in the methods described herein, particularly affinity for an epitope which binds to anti-dsDNA antibodies. Accordingly, the kits of such embodiments contain (*i.e.*, comprise) one or more dsDNA epitopes, preferably polynucleotides (preferably, double stranded (ds) DNA molecules) comprising an epitope which binds to an anti-dsDNA antibody from an individual (and the epitope-containing polynucleotide binds to an anti-dsDNA antibody from an individual). Accordingly, the kits comprise a molecule or moiety comprising a dsDNA epitope, such as any described herein. In one embodiment, the kit comprises a polynucleotide with (comprising) the sequence (or, alternatively, consisting essentially of or consisting of the sequence) ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) (with or without its complement). In certain embodiments the dsDNA epitopes are

not part of a conjugate with a non-immunogenic valency platform molecule. In other embodiments, the kits comprise the conjugates described herein, with instructions for using the conjugate to detect affinity of an individual's anti-dsDNA antibodies for the conjugate. Preferably, the conjugate is LJP 394.

Please replace paragraph **[0185]** beginning on p. 67 with the following:

[0185] In those embodiments comprising materials for testing antibody affinity, the dsDNA epitope(s) of the kit, preferably a polynucleotide(s) of the kit (whether in free form or attached to a conjugate or other matrix), generally contains, or alternatively consists of, the epitope that will be or is used in treatment, or has been demonstrated to have about the same affinity for an individual's anti-dsDNA antibodies as the epitope(s) that will be used in treatment. In other embodiments, the kits comprising a dsDNA epitope whose affinity for anti-dsDNA antibodies mimics or alternatively can be correlated to that of the dsDNA epitope to be used in treatment, such as ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1). These dsDNA epitopes can be used as "proxies" for the dsDNA epitope to be used in treatment, such as LJP 394, in assessing antibody affinity for the methods described herein.

Please replace paragraph **[0186]** beginning on p. 67 with the following:

Embodiments including materials for testing antibody affinity may comprise any appropriate means for detecting binding of the antibodies, such as a labeled anti-human antibody, when the presence of human anti-dsDNA antibodies is tested, wherein the label may be an enzyme, fluorophore, chemiluminescent material radioisotope or coenzyme. Generally, the label used will be an enzyme. Accordingly, in some embodiments, the kit(s) of the invention further comprises a label. In some embodiments, the polynucleotide in the kit(s) is conjugated to biotin. In a preferred embodiment, the dsDNA epitope (such as a polynucleotide, for example, double stranded DNA) is biotinylated. Biotinylation may also be accomplished using commercially available reagents (*i.e.*, Pharmacia; Uppsala, Sweden). In another preferred embodiment, the biotinylated dsDNA epitope comprises,

consists essentially or, or consists of is ~~5'-GTGTGTGTGTGTGTGTGTGT-3'(SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1).